June 14, 2000

Donald Barnes, Ph.D.
Science Advisory Board (1400A)
USEPA
Washington, DC 20460

Dear Dr. Barnes:

Attached are comments from the American Crop Protection Association on the SAB Executive Committee Review Draft Report, "The Application Of Cancer Risk Assessment Guidelines To Children", submitted by the Cancer Assessment Guidelines Review Subcommittee. This information is being provided to you as a Word 97 document.

Please furnish copies of all these documents to the members of the SAB Executive Committee for their review prior to the teleconference meeting that is to be held on June 16, 2000. A hard copy is also being sent for your files by FAX.

Thank you for your efforts.

Sincerely yours,

Angelina J. Duggan, Ph.D.
ACPA Director of Science Policy

Cc: Larry Dorsey, EPA
Samuel Rondberg, EPA

COMMENTS TO THE SAB CANCER RISK ASSESSMENT GUIDELINES REVIEW SUBCOMMITTEE

ON

THE APPLICATION OF THE CANCER RISK ASSESSMENT GUIDELINES TO CHILDREN

(Executive Committee Review Draft, May 19, 2000)

American Crop Protection Association
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Submitted by Angelina J. Duggan, Ph.D.
June 14, 2000

The American Crop Protection Association (ACPA) Human Health and Risk Assessment Round Table appreciates the opportunity to comment on "The Application of Cancer Risk Assessment Guidelines To Children", SAB Executive Committee Review Draft, May 19, 2000.

In a number of key areas the absence of consensus among the Subcommittee Members reflects continued disagreement among the experts on the best approach to the application of the provisions of EPA proposed cancer risk assessment guidelines to children**.**

We believe that the spectrum of adverse effects, including cancer, from the majority of pesticides currently registered for use in the United States does not differ between children and adults. Nonetheless, when credible data demonstrate increased sensitivity, we embrace appropriate modifications to the standard risk paradigms. We also believe that the majority of pesticides that have been shown to cause tumors in rodent bioassays do so through non-genotoxic (threshold) mechanisms. We support that EPA should consider the body of mechanistic data if the information are robust enough to support a threshold mode of action. While the Agency supports registrants conducting mode of action studies and welcomes mechanistic data, the amount of data, or criteria, to conclusively establish the presence or absence of a threshold, is ambiguous or often considered by EPA to be insufficient.

Some comments are indicated below:

Linear Extrapolation

The linear default approach, using the "upper bound" estimate that EPA currently uses for cancer risk assessment, is sufficiently conservative and protective of the public health of all segments of the population, including children. This is supported by published reports [Linet, 1999 #2268] that demonstrate that childhood and adult cancer rates are not increasing. In addition, a recent report [Wingo, 1999 #2269] indicates that there is no increase of cancer in any segment of the population, which suggests that exposure of children to environmental agents, is not leading to increases in cancer later in life.

Mode of Action

EPA also utilizes mode of action (MOA) data and a margin of exposure (MOE) analysis for cancer risk assessment. We believe it is appropriate for EPA to extrapolate and use MOA data developed in adults for children since overall, the body of scientific knowledge in this area supports the general conclusion that MOA is similar between children and adults. However, it is not appropriate for EPA to use linear extrapolation as a default risk assessment approach for children when sufficient MOA data is available.

Moreover, it is generally accepted that children may or may not be more sensitive to carcinogens than adults. To illustrate greater sensitivity in children, whether directly or later in life, two examples are often cited, radiation and DES exposure. These examples are used to

show that exposure to carcinogens at different stages of development influence and increase human cancer incidence. There are certain risk factors associated with radiation and DES that should be taken into consideration and used in the risk assessment process. These risk factors include genotoxicity and developmental toxicity both of results from significant endocrine involvement. When such significant factors are present, a linear extrapolation may be appropriate unless MOA are submitted present. When MOA data is available an additional safety factor may be applied if children are considered greater than 10X more sensitive than adults are. Application of a single default number; i.e., an additional 10-fold factor, to account for variability in cancer responsiveness in the general population is not warranted.

Therefore, a margin of exposure approach for cancer risk assessment in children should be used when a non-linear MOA has been demonstrated in adults. Depending on an assessment of all the available toxicology data an additional safety factor, in certain instances, may be appropriate. In most situations, however, it will not be warranted (see comment, following).

Safety Factor for Cancer Margin of Exposure Calculations

While cancer is a sensitive subject, we contend that there is no basis for increasing the standard 100-fold Safety Factor when calculating margins of exposure. The principles of toxicology do not distinguish between cancer (threshold based) and non-cancer endpoints. For situations where data describing the mode of action are sufficiently robust to support the non-linear (threshold) risk assessment, a 100-fold safety factor will be protective of the human population.

Specific comments are indicated below:

Page 4, line 15:

"Standard toxicological testing will rarely provide information that will allow a mode of action determination."

> Comment: While rodent bioassays rarely provide this information toxicological testing, may.
>
> Suggestion: "Standard rodent bioassays will rarely..."

Page 5, Line 25:

"... as a default procedure to quantify possible human cancer risks."

> Comment: The Agency characterizes the risks obtained with the low-dose extrapolation as 'probable' risks. This subtle difference in wording ('possible' to 'probable') reflects a belief that calculated risks are, in fact, real. These risks are then necessarily addressed by the Agency.

Page 12, line 28:

"...; and that people are genetically homogeneous."

> Comment: This is not an assumption made in default assessments. The Agency has imposed a 10-fold safety factor specifically to account for the non-homogeneity of people (this is acknowledged by "some Members" on page 13, line 9).

Page 15, line 4:

" ...(as well as a changing exposure scenario) are known to occur."

> Comment: We believe it is useful to separate changing behavioral or physiologic parameters from exposure. The exposure to an individual, whether it is an infant, child, or adult is a combination of the patterns of food and water intake along with the actual concentration of residues contained in these items. The fact that an infant may obtain all its nourishment from breast milk does not, in itself, characterize or confirm exposure to any one or various substances. Exposure may increase or decrease as nutrition patterns change, depending on the levels and composition of residues present in the respective foods.

References

Linet, M. S., Ries, L. A. G., Smith, M. A., Tarone, R. E., and Devesa, S. S. (1999). "Cancer surveillance series: Recent trends in childhood cancer incidence and mortality in the United States." *Journal of the National Cancer Institute,* 91, 1051-1058.

US-EPA, (1996). Federal Register Notice: "Proposed Guidelines for Carcinogen Risk Assessment." Washington, DC, 61 Federal Register 17960-18011, U.S. Environmental Protection Agency. April 23, 1996.

Wingo, P., A., ries, L. A. G., Giovino, G. A., Miller, s. W., Rosenberg, H. M., Shopland, d. R., Thun, M. J., and K., E. B. (1999). "Annual report to the nation on the status of cancer 1973 - 1996, with special section on lung cancer and tobacco smoking." *Journal of the National Cancer Institute,* 91, 675-690.